REMARKS/ARGUMENTS

Claims 42-73 and 80-91 are active in this application.

Support for the amendment to Claim 60 is found on page 18, lines 12-14 of the specification. Claim 42 is amended to clarify that the sequence in b) hybridizes to the full complementary strand of SEQ ID NO:3 and is supported on page 4, lines 11-12.

No new matter is added.

Applicants thank the Examiner for indicating the allowable subject matter in this application (item 21, page 7 of the Official Action). In view of the amendments submitted herein and the following remarks, Applicants request reconsideration of all pending rejections and allowance of all pending claims.

With respect to the election, Applicants request rejoinder again based on the following. Claim 90 (and dependent claim 91) provides a method of producing a polypeptide by expressing the cassette of Claim 86 in a cell. The cassette comprises a transgene operably linked to the nucleic acid of SEQ ID NO:4, which encodes a signal peptide. The cassette is expressed to yield a bipartite polypeptide, containing the polypeptide encoded by the transgene and the signal peptide, which is immediately cleaved in the cell (see page 18 of the present specification). Thus, the resulting product recovered is the polypeptide encoded by the transgene. Claim 73 provides a method of producing a polypeptide by culturing the recombinant cell of Claim 65, which in turn contains a vector where a transgene operably linked to the nucleic acid of Claim 42, which encodes a signal peptide. The cassette is expressed to yield a bipartite polypeptide, containing the polypeptide encoded by the transgene and the signal peptide, which is immediately cleaved in the cell (see page 18 of the present specification). Thus, the resulting product recovered is the polypeptide encoded by the transgene. As Claims 73, 90, and 91 all relate to methods of expressing a transgene, Applicants request reconsideration of the restriction imposed on Claims 90-91.

The rejection of Claims 60, 81, 83, 85, 87, and 89 under 35 U.S.C. § 112, first paragraph ("enablement") is respectfully traversed.

As amended herein, Claim 60 is amended to define the sequence as being from a Costridium strain which hybridizes to a complement of SEQ ID NO: under specific stringent conditions as described on page 5, lines 13-15 of the specification "advantageously, "hybridizing" sequences are sequences which hybridize under stringent conditions and which thus have a high degree of structural homology with a sequence under consideration." Further, the sequences that hybridize under these conditions and have the requisite activity. Further, Claim 60 is amended to define central structural features as defined in the specification on page 18, lines 12-14: "comprising a hydrophobic region bordered by charged amino acids."

Accordingly, withdrawal of this ground of rejection is requested.

The rejection of Claims 60, 81, 83, 85, 87, and 89 under 35 U.S.C. § 102(b) over Hunter et al. is respectfully traversed.

The sequence described in Hunter et al. is 90 nucleotides long, i.e., 30 amino acids (and provides only a 9 nucleotide region of overlap to the sequence in SEQ ID NO: 4, which is 90 nucleotides in length.

Hunter et al, however, do not describe the purified nucleic acid claimed in the amended Claim 60. Specifically, Hunter et al do not describe a sequence from a Clostridium strain, which hybridizes to SEQ ID NO:4, encodes a peptide that functions as a secretion signal peptide, AND comprises a hydrophobic region bordered by charged amino acids.

As known in the art, charged amino acids include (see the attached copy of Alberts et al, Molecular Biology of the Cell, page 131:

(1) positively charged amino acids: glutamic acid (E) and aspartic acid (D); and

(2) negatively charged amino acids: histidine (H), arginine (R), and lysine (K).

Hunter et al do not describe a peptide which comprises a hydrophobic region bordered by charged amino acids as claimed. Rather, Hunter et al describe the presence of 3 lysine residues in the N-terminal portion of the signal peptide depicted in Figure 2 (page 3961) but uncharged amino acids at the C-terminal end.

Accordingly, withdrawal of this ground of rejection is requested.

The rejection of Claim 42(b) and Claims 50-51, and 54-55(b) under 35 U.S.C. § 102(b) in view of Graves et al is respectfully traversed.

Graves et al describes a promoter sequence of the Fd gene in *C. pasteurianum* (page 11413, line 20 and Figure 7) and includes a (-35) region and a pribnow region (-10). However, Graves et al do not describe the purified nucleic acid as claimed in the amended Claim 42 (b) submitted herein, i.e., hybridizing under stringent conditions to all of the complementary strand of SEQ ID NO:3.

Accordingly, withdrawal of this ground of rejection is requested.

The rejection of Claims 42(b), 45-73, 81, 83, 85, 87 and 89 (b) under 35 U.S.C. § 102(b) in view of Brown is respectfully traversed.

In the Abstract of Brown (cited in the Office Action), Brown describes incorporating promoter elements for transcription and translation into an expression cassette to produce recombinant non-toxic fragments of C. botulinum neurotoxin A (BoNT/A). Brown also describes including a "secretory leader sequence for export of recombinant protein." (last paragraph of the Abstract). Brown does not describe what type of secretory leader sequence

was used and, particularly, does not describe that the secretory leader sequence is of a Clostridum strain.

The Examiner has alleged that Brown "inherently" describe a portion of SEQ ID NO:3 and 4 that would hybridize to these sequences (see page 9 of the Official Action). However, the Examiner has provided no proof of this. Rather, the Examiner is using Applicants' disclosure against them. As noted by the court in *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323 (CCPA 1981), the mere fact that a certain thing may result from a given set of circumstances is not sufficient to prove inherency. Inherency may not be established by probabilities or possibilities. Something that is inherent must inevitably be the result each and every time.

It is by now well settled that the burden of establishing a *prima facie* case of anticipation resides with the Patent and Trademark Office. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), quoting *In re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967).

As noted by the Board of Patent Appeals and Interferences in *Ex parte Skinner*, 2 USPQ2d 1788, before an Examiner can switch the burden of proof of showing non-inherency to the applicant, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art. In this case, the Examiner has provided no such evidence. Accordingly, the rejection should be withdrawn

Finally, Applicants request allowance of this application.

Respectfully submitted,

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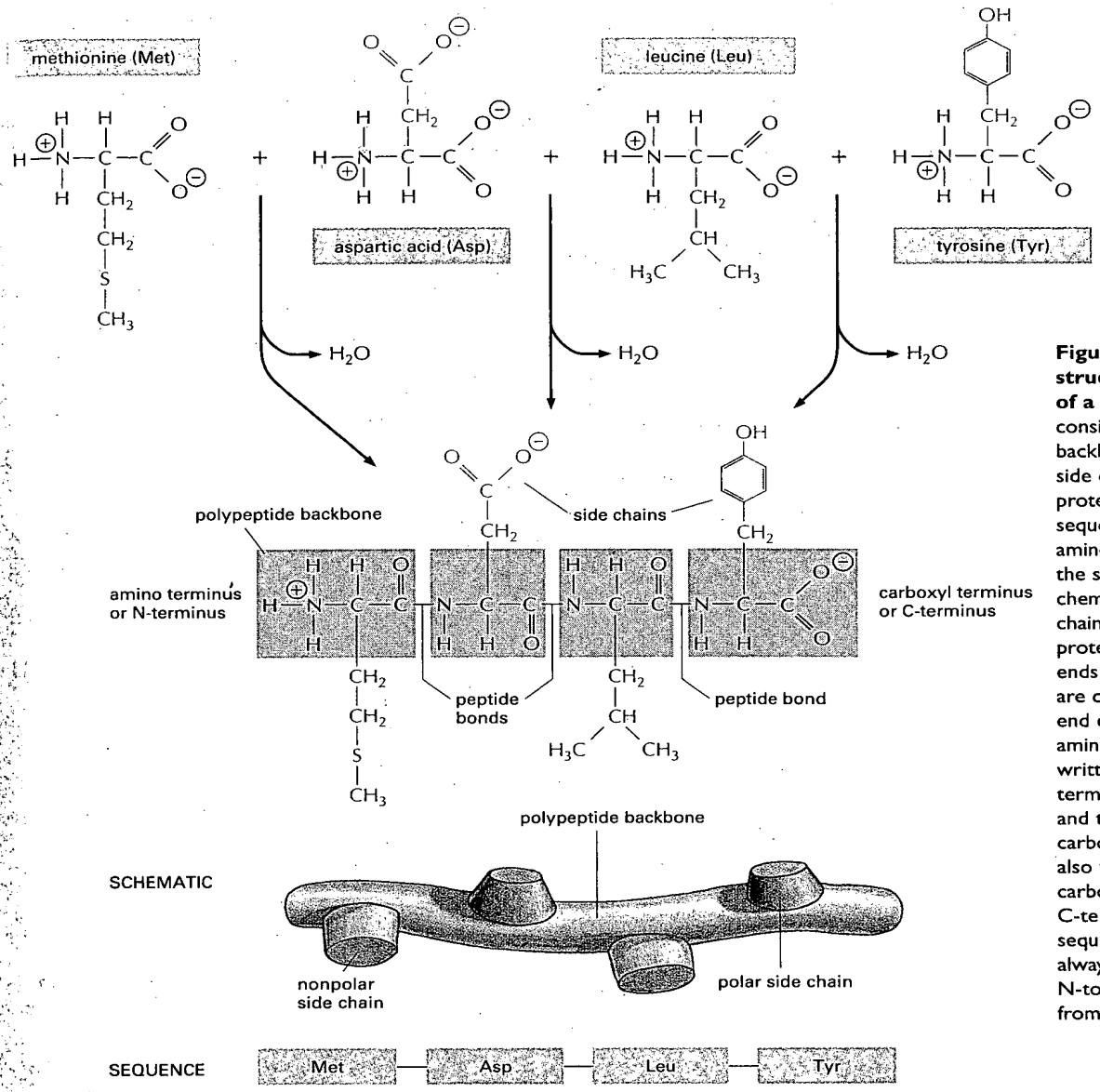

Figure 3–2 The structural components of a protein. A protein consists of a polypeptide backbone with attached side chains. Each type of protein differs in its sequence and number of amino acids; therefore, it is the sequence of the chemically different side chains that makes each protein distinct. The two ends of a polypeptide chain are chemically different: the end carrying the free amino group (NH_3^+, also written NH_2) is the amino terminus, or N-terminus, and that carrying the free carboxyl group (COO^-, also written COOH) is the carboxyl terminus or C-terminus. The amino acid sequence of a protein is always presented in the N-to-C direction, reading from left to right.

AMINO ACID			SIDE CHAIN
Aspartic acid	Asp	D	negative
Glutamic acid	Glu	E	negative
Arginine	Arg	R	positive
Lysine	Lys	K	positive
Histidine	His	H	positive
Asparagine	Asn	N	uncharged polar
Glutamine	Gln	Q	uncharged polar
Serine	Ser	S	uncharged polar
Threonine	Thr	T	uncharged polar
Tyrosine	Tyr	Y	uncharged polar

POLAR AMINO ACIDS

AMINO ACID			SIDE CHAIN
Alanine	Ala	A	nonpolar
Glycine	Gly	G	nonpolar
Valine	Val	V	nonpolar
Leucine	Leu	L	nonpolar
Isoleucine	Ile	I	nonpolar
Proline	Pro	P	nonpolar
Phenylalanine	Phe	F	nonpolar
Methionine	Met	M	nonpolar
Tryptophan	Trp	W	nonpolar
Cysteine	Cys	C	nonpolar

NONPOLAR AMINO ACIDS

Figure 3–3 The 20 amino acids found in proteins. Both three-letter and one-letter abbreviations are listed. As shown, there are equal numbers of polar and nonpolar side chains. For their atomic structures, see Panel 3–1 (pp. 132–133).